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Failure of Vancomycin Prophylaxis and Treatment for *Actinobacillus actinomycetemcomitans* Endocarditis

ROBERT H. K. ENG,[1]* SHARON M. SMITH,[1] ELLIE J. C. GOLDSTEIN,[2] KENNETH T. MIYASAKI,[3] SAW-EAN QUAH,[1] AND FRANK BUCCINI[1]

Infectious Disease Section, Medical Service, and Microbiology Section, Laboratory Service, Veterans Administration Medical Center, East Orange, New Jersey 07019[1]; R. M. Alden Laboratory, Los Angeles, California 90049[2]; and Department of Oral Biology, School of Dentistry, University of New York, Buffalo, New York 14226[3]

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Reported is a case of *Actinobacillus actinomycetemcomitans* endocarditis which developed after dental prophylaxis with vancomycin and erythromycin. In vitro results indicated that this isolate and 20 additional isolates were resistant to vancomycin and that potentially useful bactericidal antibiotics for the prophylaxis and treatment of *A. actinomycetemcomitans* infections included gentamicin, sulfamethoxazole-trimethoprim, cefotaxime, and ciprofloxacin.

Sporadic cases of endocarditis prophylaxis failures have been reported for both susceptible and resistant organisms (3, 7, 12; D. T. Durack, E. L. Kaplan, and A. L. Bisno, Clin. Res. 29:384A, 1981). We describe an unusual case of endocarditis caused by a vancomycin prophylaxis failure. Possible reasons for the antibiotic failure are discussed.

Case report. A 61-year-old man was admitted with fever, chills, and painful swelling of finger pulps and toes. He had had prosthetic Bjork-Shiley mitral and Starr-Edwards aortic valves inserted 10 years ago because of rheumatic valvular stenosis. In the preceding 5 months, he had had six tooth extractions. He had received 0.5 g of vancomycin intravenously during each extraction, 0.5 g of erythromycin orally prior to the procedure, and 0.5 g of erythromycin every 6 h for the next 24 h. Penicillin was not given because of a prior episode of type I penicillin allergy.

On physical examination, the rectal temperature was 102.8°F (ca. 39.3°C), the blood pressure was 100/70 mm Hg, the pulse rate was 92/min, and the respiratory rate was 22/min. The peripheral leukocyte count was 8,400/mm^3, with 2% band forms. More than 25 blood cultures with the BACTEC system showed no growth up to 14 days of incubation.

The pyrexia continued, and vancomycin (2 g per day) was empirically begun, with no clinical response for the next 7 days. On hospital day 29, the patient developed extreme hyperthermia (107°F [ca. 41.7°C]) and expired.

An autopsy revealed vegetations on the posterior leaflet of the artificial mitral valve and a 2.5-cm valvular dehiscence. Blood cultures incubated for longer than 14 days began to grow small gram-negative rods which were subsequently identified as *Actinobacillus actinomycetemcomitans* and confirmed by the Centers for Disease Control, Atlanta, Ga. At least one set of blood cultures was positive from the periods prior to vancomycin therapy, during vancomycin therapy, and just prior to death.

Bacterial isolates. This isolate and 20 additional isolates were studied. Fifteen were from the Department of Oral Biology and Periodontal Diseases Clinical Research Center, State University of New York, Buffalo, and were described by Zambon et al. (17). Of the 15, 2 were National Collection of Type Cultures, Central Public Health Laboratory, London, England, strains, and 3 were American Type Culture Collection, Rockville, Md., strains. The remaining five isolates were from oral cavities or bite wounds of patients. The isolates are referred to as *A. actinomycetemcomitans* in this report despite a recently proposed reclassification to the genus *Haemophilus* (11).

Susceptibility testing. The isolates were grown in 5% CO_2 on chocolate agar (BBL Microbiology Systems, Cockeysville, Md.) and in liquid medium (pH 7.2) composed (per liter) of protease peptone (BBL) (5 g), yeast extract (Difco Laboratories, Detroit, Mich.) (5 g), sodium chloride (5 g), potassium diphosphate (5 g), and glucose (2 g) (8). For studies involving sulfamethoxazole-trimethoprim, thymidine kinase (Burroughs Wellcome Co., Research Triangle Park, N.C.) was added to a final activity of 1.0 U/ml to eliminate free thymidine. The antibiotics used were obtained from their manufacturers and were dissolved in accordance with the instructions of the manufacturers.

Susceptibility tests were performed by the macrobroth dilution method (9). The MICs were determined after 48 h of incubation. The MBC was the lowest concentration which produced 99.9% killing of the inoculum, as determined with 0.1-ml subcultures of the homogenized tube contents on chocolate agar.

Killing kinetics were determined with an inoculum of 5×10^5 CFU/ml in 5.0 ml of liquid medium containing antibiotics at four times the MICs. At 0, 6, and 24 h of incubation, a 1-ml portion was removed from each tube and homogenized for five min in a Pott-Elvehjem hand grinder. Portions were then quantitatively subcultured on chocolate agar. After 48 h, the number of colonies was recorded.

Susceptibility results. The MICs of vancomycin, penicillin, erythromycin, and ciprofloxacin for the isolate from the patient were 50, 0.4, 4.0, and 0.2 μg/ml, respectively. The susceptibility results for the 20 additional isolates are shown in Table 1. Only vancomycin (MIC, 16 to 120 μg/ml) failed to inhibit or kill the isolates at attainable blood levels. Cefotaxime, cefoxitin, sulfamethoxazole-trimethoprim, and erythromycin were bactericidal, although less so than penicillin, gentamicin, and ciprofloxacin (Table 1).

The current recommendations on antibiotic prophylaxis and treatment of endocarditis caused by mouth organisms are based primarily on studies of the viridans streptococci

* Corresponding author.

TABLE 1. Results of susceptibility testing and killing kinetics for the 20 additional isolates

Antibiotic	MIC		Log change in CFU/ml in 24 h
	Range	Mean	
Vancomycin	16.0–120.0	50.1	None or an increase
Penicillin G	0.02–4.0	0.8	−4.1
Cefotaxime	0.02–0.5	0.06	−3.0
Cefoxitin	0.2–4.0	0.83	−2.8
Gentamicin	0.1–10.0	1.26	−4.2
Erythromycin	0.12–4.0	2.1	−3.5
Sulfamethoxazole-trimethoprim	1.6–100.0/0.08–5.0	20.0/1.0	−3.3
Ciprofloxacin	0.001–0.5	0.02	−4.2

(1). These streptococci are the most frequently found organisms in bacteremia or endocarditis related to dental manipulations (2, 4). Blood culture studies during dental procedures would support this, but such studies cannot accurately assess the frequency of procedure-related bacteremia caused by fastidious organisms. Since our isolate required an incubation period of more than 14 days to detect growth, bacteremia caused by such fastidious organisms must be underestimated by various published studies (2, 4).

Penicillin appears to be a logical choice for dental prophylaxis because of its good inhibitory and bactericidal activities for streptococci, oral anaerobes, and most fastidious gram-negative rods (*A. actinomycetemcomitans*, *Eikenella corrodens*, *Cardiobacterium hominis*, *Haemophilus aphrophilus*, and *Haemophilus paraphrophilus*). For patients who are allergic to penicillin, alternatives which are much less acceptable have been used. Erythromycin, generally thought to be bacteriostatic (5), has been reported to fail in the prophylaxis of infections caused by erythromycin-susceptible and -resistant streptococci (3). Erythromycin has only variable activity for *A. actinomycetemcomitans* (13), and the MIC for our isolate was 4.0 μg/ml (intermediate susceptibility), a result which attests to this variability. Vancomycin, another alternative antibiotic, has poor activity for *A. actinomycetemcomitans* (12) and is contraindicated for localized juvenile periodontitis because of its lack of activity for this species (14, 15). In addition, vancomycin has poor antimicrobial activity for many other species of mouth flora, such as *Neisseria* spp. and *Haemophilus aphrophilus* (6, 10, 16). Ciprofloxacin had good activity for *A. actinomycetemcomitans*. The combined advantages of oral absorption, high potency, and rapid bactericidal activity make ciprofloxacin an attractive alternative for the prophylaxis and treatment of *A. actinomycetemcomitans* infections. Ciprofloxacin may be superior to penicillin G, since the latter is known to have high MICs for some strains (13); in our study, MICs of as high as 4 μg/ml were observed.

Recognition of the gap in the activity spectrum of vancomycin can perhaps be lifesaving in *A. actinomycetemcomitans* endocarditis. The slow growth of this organism will not enable early identification or susceptibility testing, and empirical therapy is most often necessary. The present logical alternatives may include sulfamethoxazole-trimethoprim, broad-spectrum cephalosporins (for patients not allergic to cephalosporins), and gentamicin. Quinolones show promise for both prophylaxis and treatment but need further evaluation.

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